REMARKS

The amendment at page 7, line 7 is supported by original claim 4 (after correcting the obvious typographical errors in "dentrose" and mulodextrose" - where --dextrose-- and --maltodextrin-- were intended). No new matter has been added. The amendments merely correct minor typographical and grammatical errors.

The application is considered in good and proper form for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

PARIKH et al.

Application No. 09/443,863 Art Unit: 1615

Filed: November 19, 1999 Examiner: G. Kishore

For: DISPERSIBLE PHPOSPHOLIPID STABILIZED MICROPARTICLES

AMENDMENTS TO SPECIFICATION AND CLAIMS

Amendments to the paragraph beginning at page 3, line 9:

~~In~~ US Patent 5,302,401 describes a method to reduce particle size growth during lyophilization. It discloses a composition containing particles having a surface modifier adsorbed onto the surface together with a cryoprotectant, the cryoprotectant present in an amount sufficient to form a nanoparticle-cryoprotectant composition. A preferred surface modifier is polyvinylpyrrolidone, and a preferred cryoprotectant is a carbohydrate such as sucrose. Also described are methods of making particles having a surface modifier adsorbed on to the surface and a cryoprotectant associated with it. The patent refers specifically to 5% Danazol with 1.5% PVP and sucrose (2%) or mannitol (2%) as the cryoprotectant. Thus while various ~~cyroprotectants~~ cryoprotectants are available and function adequately to protect the active agent during lyophilization, the solid product that results is often difficult to redisperse in aqueous media.

Amendments to the paragraph beginning at page 3, line 24:

This invention is directed to an improvement in the dispersibility of micronized particles through the specific selection of excipients and methodology necessary to recover the primary particles. Inherent in this approach is the ability to produce stable aqueous suspensions of micron or submicron particles of water insoluble or poorly water-soluble compounds. These particles, which are required in the practice of the present invention, can be prepared according to the methods disclosed in U.S. Pat. No. 5,091,187 and 5,091,188 as

well as WO 98/07414, whose disclosure is incorporated herein by reference. Briefly, water insoluble or poorly soluble compounds are dispersed in an aqueous medium in the presence of surface modifying agents or combinations of agents of which at least one is a phospholipid adsorbed on the surface thereof. Particle fragmentation occurs when the aforementioned suspension is subjected to stress as a result of processing with the use of various methods known in the art including, but not limited to, sonication, milling, homogenization, microfluidization, and antisolvent and solvent precipitation. The particle so produced is referred to as a microparticle which is defined herein as a solid particle of irregular, non-spherical or spherical shape having a nominal diameter of from nanometers to micrometers on to which is adsorbed ~~a~~ at least one surface modifying agent of which one is a phospholipid.

Amendments to the paragraph beginning at page 4, line 24:

The present invention comprises a rapidly disintegrating solid dosage form for water insoluble compounds, which releases primary particles stabilized with one or more surface modifiers, including but not limited to ~~phosphlipids~~ phospholipids. Examples of some preferred water-insoluble drugs include antifungal agents, immunosuppressive and immunoactive agents, antiviral agents, antineoplastic agents, analgesic and antiinflammatory agents, antibiotics, antiepileptics, anesthetics, hypnotics, sedatives, antipsychotic agents, neuroleptic agents, antidepressants, anxiolytics, anticonvulsant agents, antagonists, neuron blocking agents, anticholinergic and cholinomimetic agents, antimuscarinic and muscarinic agents, antiadrenergic ~~and~~ agents, ~~antarrhythmics~~ antiarrhythmics, antihypertensive agents, hormones, and nutrients. A detailed description of these drugs may be found in Remington's Pharmaceutical Sciences, 18th Edition, 1990, Mack Publishing Co., PA. The concentration of the water insoluble ingredient in the aqueous suspension can vary between 0.1% w/w and 60% w/w, preferably between 5% w/w and 30% w/w.

Amendments to the paragraph beginning at page 5, line 8:

The water insoluble compound is first prepared as an aqueous suspension in the presence of one or more surface stabilizing agents, of which at least one is a phospholipid. The phospholipid may be any natural or synthetic phospholipid, including but not limited to, phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, ~~phosphatidylinoistol~~ phosphatidylinositol, phosphatidylglycerol, phosphatidic acid, lysophospholipids, egg or soybean phospholipid or a combination thereof. The phospholipid may be salted or desalted,

hydrogenated or partially hydrogenated or natural, semisynthetic or synthetic. The concentration of the phospholipid ingredient in the aqueous suspension can vary between 0.1% w/w and 90% w/w, preferably between 0.5% w/w and 50% w/w and more preferably between 1% w/w and 20% w/w.

Amendments to the paragraph beginning at page 5, line 17:

Examples of some suitable second and additional surface modifiers include: (a) natural surfactants such as casein, gelatin, natural phospholipids, tragacanth, waxes, enteric resins, paraffin, acacia, ~~gelatin,~~ and cholesterol, (b) nonionic surfactants such as polyoxyethylene fatty alcohol ethers, sorbitan fatty acid esters, polyoxyethylene fatty acid esters, sorbitan esters, glycerol monostearate, polyethylene glycols, cetyl alcohol, cetostearyl alcohol, stearyl alcohol, poloxamers, polaxamines, methylcellulose, hydroxycellulose, ~~hydroxy propylcellulose~~ hydroxypropyl cellulose, ~~hydroxy propylmethylcellulose~~ hydroxypropyl methylcellulose, noncrystalline cellulose, and synthetic phospholipids, (c) anionic surfactants such as potassium laurate, triethanolamine stearate, sodium lauryl sulfate, alkyl polyoxyethylene sulfates, sodium alginate, dioctyl sodium sulfosuccinate, negatively charged phospholipids (phosphatidyl glycerol, ~~phosphatidyl inositol~~ phosphatidylinositol, phosphatidylserine, phosphatidic acid and their salts), and negatively charged glyceryl esters, sodium carboxymethylcellulose, and calcium carboxymethylcellulose, (d) cationic surfactants such as quaternary ammonium compounds, benzalkonium chloride, cetyltrimethylammonium bromide, and lauryldimethylbenzyl-ammonium chloride, (e) colloidal clays such as bentonite and veegum. A detailed description of these surfactants may be found in Remington's Pharmaceutical Sciences, 18th Edition, 1990 Mack Publishing Co., PA; and Theory and Practice of Industrial Pharmacy, Lachman et al., 1986. The concentration of additional surfactants in the aqueous suspension can vary between 0.1% w/w and 90% w/w, preferably between 0.5% w/w and 50% w/w and more preferably between 1% w/w and 20% w/w. These surfactants may be either added initially during compounding or added post processing prior to freeze-drying or a combination of both depending on the nature, concentration and number of the surfactant(s).

Amendments to the paragraph beginning at page 6, line 29:

The resulting homogeneous suspension of microparticles stabilized by one or more surface modifiers is then mixed with bulking and/or releasing agents (dry or as an aqueous solution) and is then dried. The bulking or matrix-forming agent provides a mass in which the particles of drug are embedded or ~~retain~~ retained. The release agent assists in disintegration

of the matrix when it contacts aqueous media. The bulking/releasing agents are chosen in order to produce a support matrix that, upon drying, will yield rapidly dispersible tablets that release the primary particles upon reconstitution in an aqueous medium. Examples of matrix-forming agents include (a) saccharides and polysaccharides such as mannitol, trehalose, lactose, sucrose, sorbitol, maltose, dextrose and maltodextrin; (b) humectants such as glycerol, propylene glycol, and polyethylene glycol; (c) natural or synthetic polymers such as gelatin, dextran, starches, polyvinylpyrrolidone, poloxamers, and acrylates; (d) inorganic additives such as colloidal silica, tribasic calcium phosphate and; (e) cellulose based polymers such as microcrystalline cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, and methylcelluloses. Matrix forming agents may be added prior to producing the micronized particles of the therapeutic agent (formulation) or to the homogeneous suspension of microparticles prior to freeze-drying. The concentration of the matrix forming agents in the aqueous suspension can vary between 0.1% w/w and 90% w/w, preferably between 0.5% w/w and 50% w/w and more preferably between 1% w/w and 20% w/w.

Amendments to existing claims:

50. (Amended) A process for the preparation of a rapidly disintegrating solid dosage form capable of forming a stable suspension without irreversible particle aggregation and/or particle agglomeration or particle growth comprising:

a) forming an admixture of a stable aqueous homogenous suspension of micronized surface stabilized primary particles of a water-insoluble or poorly water-soluble drug with a matrix-forming bulking/releasing agent or a mixture of matrix-forming bulking and releasing agents, wherein said stable aqueous ~~primary particle~~ homogeneous suspension has a particle size of about 10 μm or less, and each primary particle is a solid drug particle on to which is adsorbed at least one surface modifying agent of which one is a phospholipid~~,~~;

b) drying said admixture to produce a ~~solidified suspension~~ solid of said surface stabilized primary particles dispersed and embedded throughout a support matrix of said matrix-forming agent or agents, wherein said matrix dissolves or substantially disperses in a rapid disintegration time when in contact with an aqueous environment to release said surface stabilized primary particles into said aqueous environment as a suspension without irreversible particle aggregation and/or particle agglomeration and without particle size growth;

c) optionally course milling and blending said ~~solidified suspension~~ solid with one or more pharmaceutically acceptable excipients to provide a dried powder; and

d) forming said ~~dried material~~ solid or said dried powder into a solid dosage form.

52. (Amended) The process of claim 50, wherein the matrix-forming bulking/releasing agent is selected from the group consisting of mannitol; trehalose; sorbitol; maltose; and combinations thereof; combinations of mannitol, trehalose, sorbitol, and maltose with lactose; combinations of mannitol, trehalose, sorbitol, maltose, and lactose with sucrose; and combinations thereof with a pH buffering salt.

53. (Amended) The process of claim 50, wherein the matrix-forming bulking/releasing agent is selected from the group consisting of mannitol; trehalose; sorbitol; and maltose; combinations of mannitol, trehalose, sorbitol, and maltose with lactose; combinations of mannitol, trehalose, sorbitol, maltose, and lactose with sucrose; microcrystalline cellulose; hydroxymethyl cellulose; hydroxypropyl cellulose; methylcellulose; and combinations thereof, and combinations thereof with a pH buffering salt.

54. (Amended) The process of claim 50, wherein the matrix-forming agent is present in an amount between 0.1 % w/w and 90% w/w of the aqueous suspension.

56. (Amended) The process of claim 50, wherein the drug is selected from the group consisting of antifungal agents, immunosuppressive agents, immunoactive agents, antiviral agents, antineoplastic agents, analgesic agents, antiinflammatory agents, antibiotic agents, antiepileptic agents, anesthetic agents, hypnotic agents, sedative agents, antipsychotic agents, neuroleptic agents, antidepressant agents, anxiolytic agents, anticonvulsant agents, antagonist agents, neuron blocking agents, anticholinergic agents, cholinomimetic agents, antimuscarinic agents, muscarinic agents, anti adrenergic agents, ~~antarrhythmic~~ antiarrhythmic agents, antihypertensive agents, hormones, and nutrients.

58. (Amended) The process of claim 50, wherein the drug is present in an amount between 0.1% w/w and 60% w/w of the aqueous suspension.

61. (Amended) The process of claim 50, wherein the phospholipid is selected from the group consisting of phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, ~~phosphatidylinoistol~~ phosphatidylinositol, phosphatidylglycerol, phosphatidic acid, a lysophospholipid, and combinations thereof.

62. (Amended) The process of claim 50, wherein the surface modifier is selected from the group consisting of ~~pharmaceutically acceptable~~ pharmaceutically acceptable nonionic

surfactants, pharmaceutically acceptable anionic surfactants, and pharmaceutically acceptable cationic surfactants.

66. (Amended) The process of claim 50, wherein the surface modifier is selected from the ~~group~~ group consisting of potassium laurate, triethanolamine stearate, sodium lauryl sulfate, an alkyl polyoxyethylene sulfate, sodium alginate, sodium deoxycholate, dioctyl sodium sulfosuccinate, a negatively charged glyceryl ester, sodium carboxymethylcellulose, calcium carboxymethylcellulose, and combinations thereof.

68. (Amended) The process of claim 50, wherein the surface modifier is present in an amount between 0.5% w/w and 50% w/w of the aqueous suspension.

73. (Amended) A process for the preparation of a rapidly disintegrating solid dosage form capable of forming a stable suspension without irreversible particle aggregation and/or particle agglomeration or particle growth comprising:

a) forming an admixture of a stable aqueous homogenous suspension of micronized surface stabilized primary particles of a water-insoluble or poorly water-soluble drug with a matrix-forming bulking/releasing agent or a mixture of matrix-forming bulking and releasing agents, wherein said stable aqueous ~~primary particle~~ homogeneous suspension has a particle size of about 10 μm or less, each primary particle is a solid drug particle on to which is adsorbed at least one surface modifying agent of which one is a phospholipid;

b) distributing the admixture of (a) into unit dosage form molds; and

c) freeze-drying said admixture in said unit dosage form molds to produce a ~~solidified suspension~~ solid dosage form of said surface stabilized primary particles dispersed and embedded throughout a support matrix of said matrix-forming agent or agents, wherein said matrix dissolves or substantially disperses in a rapid disintegration time when in contact with an aqueous environment to release said surface stabilized primary particles into said aqueous environment as a suspension without irreversible particle aggregation and/or particle agglomeration and without particle size growth.

75. (Amended) The process of claim 73, wherein the matrix-forming bulking/releasing agent is selected from the group consisting of mannitol; trehalose; sorbitol; maltose; and combinations thereof; combinations of mannitol, trehalose, sorbitol, and maltose with lactose; combinations of mannitol, trehalose, sorbitol, maltose, and lactose with sucrose; and combinations thereof with a pH buffering salt.

76. (Amended) The process of claim 73, wherein the matrix-forming bulking/releasing agent is selected from the group consisting of mannitol; trehalose; sorbitol; and maltose; combinations of mannitol, trehalose, sorbitol, and maltose with lactose; combinations of mannitol, trehalose, sorbitol, maltose, and lactose with sucrose; microcrystalline cellulose; hydroxymethyl cellulose; hydroxypropyl cellulose; methylcellulose; combinations thereof, and combinations thereof with a pH buffering salt.

77. (Amended) The process of claim 73, wherein the matrix-forming agent is present in an amount between 0.1 % w/w and 90% w/w of the aqueous suspension.

79. (Amended) The process of claim 73, wherein the drug is selected from the group consisting of antifungal agents, immunosuppressive agents, immunoactive agents, antiviral agents, antineoplastic agents, analgesic agents, antiinflammatory agents, antibiotic agents, antiepileptic agents, anesthetic agents, hypnotic agents, sedative agents, antipsychotic agents, neuroleptic agents, antidepressant agents, anxiolytic agents, anticonvulsant agents, antagonist agents, neuron blocking agents, anticholinergic agents, cholinomimetic agents, antimuscarinic agents, muscarinic agents, anti adrenergic agents, ~~antarrhythmic~~ antiarrhythmic agents, antihypertensive agents, hormones, and nutrients.

81. (Amended) The process of claim 73, wherein the drug is present in an amount between 0.1% w/w and 60% w/w of the aqueous suspension.

84. (Amended) The process of claim 73, wherein the phospholipid is selected from the group consisting of phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, ~~phosphatidylinoistol~~ phosphatidylinositol, phosphatidylglycerol, phosphatidic acid, a lysophospholipid, and combinations thereof.

85. (Amended) The process of claim 73, wherein the surface modifier is selected from the group consisting of ~~pharmaceutically acceptable~~ pharmaceutically acceptable nonionic surfactants, pharmaceutically acceptable anionic surfactants, and pharmaceutically acceptable cationic surfactants.

91. (Amended) The process of claim 73, wherein the surface modifier is present in an amount between 0.5% w/w and 50% w/w of the aqueous suspension.